Remarks/Arguments

Claims 1-60 are pending in the application. The Examiner has rejected all claims. In Response, Applicant has amended Claims 4, 5, 23, 24, 42 and 43.

Claims Rejections – 35 USC § 112

The Examiner has rejected Claims 4, 5, 23, 24, 42 and 43 for insufficient antecedent basis for the limitation "per receptacle" in the independent claims. The Applicant has amended the claims to provide the antecedent basis, thus the rejection is rendered moot. The Applicant requests that the rejection be withdrawn.

Claims Rejections – 35 USC § 103

Edwards

The Examiner states that Claims 1-60 under 35 U.S.C. 103(a) are unpatentable over Edwards (5,985,309). The Examiner describes in several paragraphs (beginning on page 3 carried over to page 4) the features which she believes are disclosed by Edwards. The Examiner appears to believe that Edwards discloses a genus which may embrace the particular formulations of the claimed invention although Edwards does not expressly describe the particular claimed formulations. In order to assess this, one skilled in that art must consider a number of species, in this case formulations, encompassed by the Edwards' genus taking into consideration all of the variables possible. A brief explanation of the present application will provide the necessary context for the evaluation of the Examiner's rejections.

The Applicants have developed novel insulin-containing formulations having a controllable, in particular a rapid, release profile. This rapid release profile provides a desirable alternative to injection therapy for the treatment of disease, in particular, the treatment of diabetes in humans. The formulations were chosen for their superior fast acting properties. Indeed, as disclosed in the Examples, in human clinical trials, the formulations of the instant invention were administered and compared to presently available subcutaneous injections which represent the 'gold standard' for any new

treatment for diabetes coming on the market. That is, any new therapy for diabetes will need to meet or exceed the long-practiced regime of daily subcutaneous injection. The particular formulations being claimed in Claims 1-60 were selected for their superior performance in this regard. There is no reasonable expectation that picking and choosing random ingredients from the list of possible ingredients found in Edwards would result in superior pharmacodynamics when the formulation is inhaled versus current conventional treatment for diabetes.

Nor is there any suggestion or motivation in Edwards that would lead one skilled in the art to select the claimed combination. There must be a reasonable likelihood of success for a claimed combination *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). There is nothing in Edwards that would suggest that the particular claimed combination of insulin and excipients in the claimed ranges would have pharmacodynamic properties which are comparable, if not superior to, those of insulin lispro and regular soluble insulin. As seen in Figure 3, the $T_{max50\%}$ was lower for all doses of inhaled insulin preparation compared to insulin lispro and regular soluble insulin. Specifically, inhaled insulin results in a faster onset of action compared with subcutaneous insulin formulations of insulin lispro and regular soluble insulin. This data establishes that the claimed combination of excipients possess superior properties for the rapid release of insulin for a patient in need thereof. Those superior properties were surprising.

In summary, while Edwards may teach compositions possessing insulin and DPPC (that is, *some* of the preferred components may be present in the formulations) the exact ingredients and their proportions confer significant differences in terms of rate of release into the patient in need of treatment. The state of the art suggests that the picking and choosing of excipients and concentration impacts important properties of formulations for use in the treatment of diabetes in humans. See for example the unique ingredients of the insulin containing but very small geometric diameter (usually 0.1 to 5 micron size) particles of Patton cited by the Examiner. Accordingly, the claimed formulation which has the result of mimicking or improving upon the "gold standard"

subcutaneous delivery of insulin is neither predictable nor expected. Thus, none of the claims of the instant invention are obvious in light of Edwards.

Kohane

On pages 5 and 6 of the Office Action, the Examiner states that claims 1-2, 12-15, 18-20, 30-36, 30-40, 50-56 and 59-60 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kohane. The Examiner states that Kohane teaches lipid-protein-sugar particles for delivery of nucleic acids. The Examiner points out that the polynucleotide encodes a protein such as insulin. It is unclear how compositions comprising polynucleotides encapsulated in a matrix of lipid, protein and sugar relates at all to the particular claimed formulation of insulin and excipients in the claimed ranges which would have pharmacodynamic properties which are comparable, if not superior to, those of insulin lispro and regular soluble insulin. It appears that the Examiner is confusing the polynucleotide which encodes insulin for the insulin itself. The fact that a polynucleotide may encode insulin does not confer the properties of insulin to the polynucleotide. The polynucleotide encoding insulin is irrelevant.

The Examiner goes on to list individual excipients which may be found in the Kohane application. Applicants point out the excipients which "lead to increased stability of the polynucleotide" would not guide a person looking for particular pharmacodynamic properties which are comparable, if not superior to, those of insulin lispro and regular soluble insulin. One looking to deliver fast onset insulin would never look to the polynucleotide encoding insulin as a treatment option.

Even if the particular excipients are disclosed in the Kohane patent, once again, the Examiner is constrained from picking and choosing among thousands of possible combinations without a teaching or suggestion to do so. Kohane lacks any such teaching or suggestion. The Examiner admits that Kohane does not exemplify a composition containing DPPC, insulin and sodium state [*sic*]. The Examiner's contention that it would have been obvious to a person of ordinary skill in the art by the mere substitution of sodium citrate for the sugar of Kohane ignores the challenges in the delivery of polynucleotides as well as the unique challenges of delivering rapid acting insulin.

The claims of the instant invention are non-obvious over Kohane.

Patton 5,997,848

On page 6 of the Office Action, the Examiner states that Claims 1-9, 12-27, 30-47 and 50-60 are rejected under 103(a) as being unpatentable over Patton (5,997,848) in view of Betbeder (6,017,513).

The Examiner states that Patton teaches systemic delivery of insulin with certain disclosed characteristics but Patton lacks the teaching of DPPC. The Examiner depends upon Betbeder to supply the missing component of DPPC and then states that combining the references would have been obvious to one skilled in the art with the reasonable expectation of producing more stable and more potent insulin powders for administration through the pulmonary system for systemic absorption.

The Examiner is focusing on the selection of excipients, ranges and properties to argue the '848 patent renders the present invention obvious. Yet, in order to select those excipients, ranges and properties, the Examiner uses hindsight and is guided by the instant application. Because the breadth as disclosed in Patton is so broad, for example, the preferable concentration range of insulin is 5-95%, the limitation is, in fact, no limitation at all. The range of 5-95% is meaningless to one skilled in the art in the context of selecting the claimed ranges possessing the pharmacodynamic properties which are comparable, if not superior to, those properties of currently available therapeutics, for example, subcutaneous injection of insulin lispro and regular soluble insulin.

Further, the Examiner is picking and choosing those parameters taught by the instant invention. This type of hindsight reconstruction is not permitted. The Examiner states that Patton prepares insulin dry powders of less than 10 microns, preferably in the range of 0.1 to 5 microns. First, with respect to the size ranges, the Examiner states that the size ranges are less than 10 microns, preferably less than in the range of 0.1 to 5 microns. In reality, the sizes of the powders in the Examples were well below 5 microns. As stated by Patton, "all of the insulin powders used in the animal studies had particle

sizes (mass median diameters) ranging between 1-3 microns." (See Table 1 and Col. 11, Line 22-32).

The Examiner states that Patton teaches delivery accomplished by inhalation of a dry powder of insulin. However, the teaching of Patton is much narrower. At best, Patton teaches a two-step method of delivering particular formulations of geometrically small insulin-containing particles. The claims of the '848 Patton patent describe a method for delivering insulin which requires **dispersing** each of the dry powder insulin doses individually into a gas stream to form dry insulin aerosols; **and inhaling** each of the dry powder insulin aerosols into an alveolar region of the lung. The two-step nature of the method is reaffirmed by the text of the specification which indicates that the powder is dispersed in a gas stream to form an aerosol, and that the aerosol is "captured in a chamber having a mouthpiece, where it is available for a *subsequent* inhalation by a patient" (Col. 3, lines 22-28, emphasis added). Similar language indicating that the aerosols are captured prior to inhalation by the patient appears in a discussion of a system suitable for dispersal of the insulin in a gas stream (see, e.g., Col. 7, line 51, through Col. 8, line 9 where it is indicated that "[a]fter a dose of the insulin powder has been captured in chamber 10, a patient P (FIG. 2b) inhales on the mouthpiece 12 to draw the aerosolized dispersion into his lungs.") Thus, the '848 Patton patent should not be given greater breadth than it actually discloses. Indeed, this specific two–step method requires formulations with suitable particle characteristics for that method.

However, even if the Examiner's assertions were true, the method of Patton simply does not render obvious the formulations of the instant invention. Nothing about the two-step method of Patton makes the claimed formulations predictable or expected. For Patton's two-step method to work, Patton's formulations and parameters do matter. Turning our attention to Column 11, lines 16-20, we observe that Patton's disclosed formulations are as follows:

	% Insulin	% Mannitol or Raffinose	% Sodium citrate	% Citric acid	MMD powder	MMD in breathing zone
1	87.9	0	11.5	0.6	2.2	1.4
2	20.0	66.0	12.4	0.6	2.8	1.9
	20.0	66.0	12.4	0.6	2.0	1.3

The criteria used by Patton to select his formulations, which vary widely, are not provided. The Examiner states that Patton discloses insulin with an optional pharmaceutical carrier and buffer, typically a citrate buffer such as sodium citrate. Patton's focus was a *method for delivering* particular formulations having particular characteristics. Again, one skilled in the art would not look to the teachings of Patton, alone or in combination, for the picking and choosing of excipients and concentration of the claimed formulations possessing the pharmacodynamic properties which are comparable, if not superior to, those properties of currently available therapeutics, for example, subcutaneous injection of insulin lispro and regular soluble insulin.

Patton in view of Betbeder

Nor does Betbeder supply what Patton lacks. The Examiner uses Betbeder to supply the teaching of DPPC. The Examiner states on page 8 of the Office Action that it would have been obvious to combine the teachings of Patton which describes dry powder particles of insulin and sodium citrate for inhalation with the teachings of Betbeder which uses DPPC as a suitable carrier for therapeutic agents "with the reasonable expectation of producing more stable and more potent insulin powders." However, the Applicants are confused as to the relevance of Betbeder's method of mucosal administration of a substance by combining the substance with a Biovector core. Although it appears in Col. 7, line 13 that DPPC is a preferred ampiphilic compound which may **be adsorbed on the surface of the core of the Biovector**, Betbeder provides no motivation to use DPPC without the Biovector core.

Even if the particular excipients of the instant invention were disclosed by combining Patton and Betbeder, once again, the Examiner is constrained from picking and choosing among possible combinations without a teaching or suggestion to do so. Both Patton and Betbeder lack any such teaching or suggestion. The Examiner admits that Patton does not exemplify a composition containing DPPC. Betbeder only suggests the inclusion of DPPC for use with the Biovector. The Examiner's contention that it would have been obvious to a person of ordinary skill in the art by the mere addition of DPPC as a "carrier for therapeutic agents" ignores the challenges of the mucosal delivery using Biovectors of Betbeder as well as the unique challenges of delivering rapid acting insulin.

There must be a reasonable likelihood of success for a claimed combination *In re Vaeck, supra* (1991). The Examiner states that one skilled in the art would have a "reasonable expectation of producing more stable and more potent insulin powders for administration through the pulmonary system." There is nothing in Patton or Betbeder that would suggest that the particular claimed combination of insulin and excipients in the claimed proportions would have pharmacodynamic properties which are comparable, if not superior to, those of insulin lispro and regular soluble insulin. The results were unpredictable and unexpected. The claims of the instant invention are non-obvious over either Patton, Betbeder or the combination thereof.

Double patenting

The Examiner has provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of co-pending Application No. 10/179,463. Applicants will amend claims as necessary once allowable subject matter has been identified in the applications.

Conclusion

In light of the foregoing amendments and remarks, Applicants believe the claims are in condition for allowance and a prompt notice to that effect is requested. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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